n18 For example, Novo's attorneys admitted that the Zn-hIA structures exist as part of a larger solution or equilibrium. *See* Tr. at 347:22-348:9.

The Court essentially adopts Novo's definition of "complex" and holds that the term "complex," as used in the claims (claims 1 and 12), is an individual molecular structure, i.e., "a chemical association state of two or more molecules held together by non-covalent bonds." n19 Next, the Court essentially adopts Novo's definition of "formulation" and holds that "formulation," in claims 2-11 and 13, means "an equilibrium containing molecules and molecular structures." Finally, the Court essentially adopts both Novo's and Lilly's definitions of "hexamer," holding that the term "hexamer" means different things in different contexts so that "complex is a hexamer" in claims 1 and 12 and "Lys<B28>Pro<B29>-human insulin is a hexamer" in claim 13 mean different things. n20 In claims 1 and 12, because it is being used in the context of individual molecules and their structure, the term "hexamer" refers to the Zn-hIA structure, i.e. "a type of complex where [*25] six molecules of human insulin analog are held together in a single structure." In claim 13, because it is being used in the context of a "formulation," which is an equilibrium, the phrase "LysPro-human insulin is a hexamer" is shorthand meaning "in the equilibrium, most of the LysPro-human insulin molecules are in Zn-hIA structures." Interestingly, at the *Markman* hearing Lilly's expert, Dr. Weiss stated that the term "hexamer" has these two competing definitions, depending on the context. n21

n19 As set forth in the text, *infra*, 1999 U.S. Dist. LEXIS 18690 *33-37, in the specification, complex refers to both a molecular structure and equilibrium, dependent upon the context. Because of the context of claims 1 and 12, complex refers to a molecular structure.

N20 The Court recognizes that having two different definitions for "hexamer" violates the general rule of claim construction that the same word should be interpreted to have the same meaning throughout the claims. *See Pitney Bowes, Inc. v. Hewlett-Packard Co.*, 182 F.3d 1298, 1310 (Fed. Cir. 1999). However, "where the language of the written description is sufficient to put a reader on notice of the different uses of a term, and where those uses are further apparent from publicly available documents referenced in the patent file, it is appropriate to depart from the normal rule of construing seemingly identical terms in the same manner." *Id.* at 1311. When a term has different meanings in different contexts, "the term must be read to correspond only to the plausible meaning in each context." *Id.* As discussed in the test, *infra*, the claim language, the specification and the prosecution history fully support the two meanings of hexamer.

[*26]

n21 THE WITNESS [Dr. Weiss]: In general the word hexamer is used in two senses in this patent. It refers, if it's not modifying anything, hexamer by itself, it refers to the hexameric self association unit. . . . If it's modifying hexamer, if it's modifying complex either in the phrase hexamer complex or such that complex is a hexamer in this adjunct title sense, then it means that the equilibrium is such that nearly all the molecules are participating in one of the hexameric self association states.

Tr. at 80:19-81:7. The Court does not rely on this extrinsic evidence in resolving the issues. Nonetheless, it takes some comfort in Dr. Weiss' testimony.

1. The Claim Language

The starting point for claim construction is the plain language of the claims. *See Smiths Indus. Medical Systems*, 183 F.3d at 1357. The claim language provides support for the Court's definitions of "complex," "hexamer," and "formulation."

First, claim 1 defines "complex" in terms of the number of molecules of hIA, the number of ions of zinc, and the number of molecules of phenolic. Because [*27] claim 1 refers only to eleven molecules, the term "complex" must refer to only an individual molecular structure, not to an equilibrium. If "complex" referred to an equilibrium, it would have to contain some of the individual molecules of hIA, zinc, and phenolics and some of the Zn-hIA structures. That is, the equilibrium would have to contain more than simply the eleven molecules listed in the claim. n22 It would not make sense for an equilibrium state to contain only the eleven molecules listed as part of the "complex."

n22 Lilly argues that the use of the term "comprising" in claim 1 means that the "com-

plex" contains more than the listed eleven molecules in the equilibrium. This argument is unpersuasive for two reasons. First, as discussed in Part IV.C, *infra*, the term "comprising" means that the "complex" can contain other types of molecules not listed, but that it can contain six, and only six, hIA molecules and two, and only two, zinc ions. Second, claim 12 has the exact same claim language as claim 1 except that it uses the closed ended "consisting of" instead of "comprising." This language means that the "complex" in claim 12 contains only the eleven listed molecules. These eleven claimed molecules by themselves could not be an equilibrium between individual molecules and the Zn-hIA structures.

[*28]

Lilly also argues that the eleven molecules listed in claim 1 refer to the relative stoichiometric proportions of the molecules in the equilibrium. However, if this argument is correct, then Lilly's other definition of "complex is a hexamer" meaning that most of the molecules in the equilibrium are be in Zn-hIA hexamers cannot also be correct. To illustrate, accept for the moment that Lilly is correct. According to Lilly's definitions, claim 1 would then claim an equilibrium having hIA molecules and Zn ions in a 6:2 ratio where most of the molecules in the equilibrium are in Zn-hIA hexamers. However, the patent specification teaches a wide range of ratios of hIA molecules to zinc ions in the equilibrium, n23 while also teaching that in each individual hexamer structure there are exactly 6 hIA molecules and exactly two zinc ions. n24 The fact that the claim recites a whole number ratio of 6:2, as opposed to some fractional ratio, strongly indicates that the claim is directed to the structure, not the equilibrium. Moreover, the most preferred embodiment in the specification teaches that in order to achieve a solution of mostly hexamers, there must be more than two zinc ions for every [*29] six molecules of hIA. n25 Therefore, the list of the eleven molecules in claim 1 does not refer to the stoichiometric ratios of these molecules in an equilibrium. Rather, it refers to the number of molecules in the structure.

n23 The specification recites a sliding scale range of the preferred concentrations of hIA molecules to zinc ions in order for the solution to have mostly hexamers. *See* '978 Patent at 4:60-67. The preferred range of hIA is from 1.2 mg/mL to 17.5 mg/mL. *See id.* The preferred concentration of zinc is 14 [mu] g/mL to 35 [mu] g/mL. Converting these weights to moles reveals a wide range of ratios of zinc ions per hIA molecules. For these calculations the molecular weight of hIA is estimated at 6000 mg/mmol, *see* 8 McGraw-Hill Encyclopedia of Science and Technology, 264 (8th ed. 1997), and the molecular weight of zinc is 65.4 mg/mmol, *see* 19 McGraw-Hill Encyclopedia of Science and Technology, 699. The following calculations illustrate the point:

Smallest Ratio of hIA to Zn:

hIA: (1.2 mg/mL)(mmol/6000 mg) = 2.0 x 10<-4> mmol/mL
Zn: (35 [mu] g/mL)(mg/1000 [mu]g)(mmol/65.4 mg) = 5.35 x 10<-4> mmol/mL
Ratio: 2.0 hIA:5.35 Zn = 6.0 hIA:16.0 Zn

Largest Ratio of hIA to Zn:

hIA: (17.5 mg/mL)(mmol/6000 mg) = 29.0 x 10<-4> mmol/mL
Zn: (14 [mu] g/mL)(mg/1000 [mu] g)(mmol/65.4 mg) = 2.14 x 10<-4> mmol/mL
Ratio: 29.0 hIA:2.14 Zn = 6.0 hIA:0.4 Zn

[*30]

n24 *See* '978 patent at 4:67-5:1.

n25 Figure 3 illustrates that in order to achieve mostly hexamers, there must be an hIA concentration of 3.5 mg/mL. In this solution, the ratio of Zn ions to hIA molecules is 0.5. *See '978* Patent at 3:37-38. Thus, the ration of hIA to Zn is 6.0 hIA:3.0 Zn, which is more than 2 zinc ions for every six molecules of hIA.

In contrast, claim 13 defines a "formulation" in terms of the concentrations of the hIA, zinc, and phenolics in solution. Because claim 13 refers to the concentrations in solution, and not the number of molecules, the

term "formulation" must refer to the equilibrium containing molecules and molecular structures. Moreover, the proportion of the hIA molecules to zinc ions is not the 6:2 ratio of these species in a single Zn-hIA structure. n26 Therefore, the term "formulation" must refer to more than just a molecular structure; it must refer to the overall equilibrium.

n26 Claim 13 claims a ratio of roughly 2.5 zinc ions to 6 hIA molecules.

[*31]

Because claim 1 claims a "complex," i.e., a molecular structure, the term "hexamer" is used in the structural sense to mean a single Zn-hIA structure. It would make no sense for the claim to read that most of the complexes are in the Zn-hIA molecular structure because the claim only lists the exact number of molecules needed to form one Zn-hIA molecular structure. It follows that "hexamer" is being used in the structural sense.

Because claim 13 claims a "formulation," i.e., an equilibrium, the phrase "Lys<B28>Pro<B29>-human insulin is a hexamer" means that most of the Lys<B28>Pro<B29>-human insulin molecules are associated into Zn-hIA molecular structures. It would make no sense for "hexamer" to have a structural meaning in this claim because it claims 3.5 mg/mL Lys<B28>Pro<B29>-human insulin, or about 3.5 x 10 <17> molecules per mL of solution. It would be absurd to say that this number of molecules "is a molecular structure." Rather, in the context of a "formulation" or equilibrium, it makes more sense for "hexamer" to have its shorthand meaning as most of the LysPro-human insulin molecules are in Zn-hIA structures.

Lilly counters that, in claim 1, the term "hexamer" cannot refer [*32] to a single Zn-hIA structure because the term "hexamer" would be superfluous. It further argues that "hexamer" cannot mean an individual molecular structure of six hIA molecules, two zinc ions, and at least three phenolic molecules because the "complex" is already defined as a molecular structure containing these eleven components. However, Lilly's position cannot withstand close scrutiny because "complex" is a general term referring to all types of molecular structures, including monomers, dimers, tetramers, and hexamers (Zn-hIA structures). As such, the term "hexamer" refers to a specific type of complex where six of the hIA molecules are bound together in a single structure. The term "hexamer" is not superfluous because a "complex, which comprises: six molecules of human insulin analog" could be a complex of three dimers or one hexamer. Therefore, "hexamer" has independent meaning as a complex where the six hIA molecules are bound together in a single structure.

Lilly further argues that "complex" must refer to the equilibrium state because claim 10 claims using a "complex" to treat a patient and a patient can only be treated with an equilibrium solution. n27 However, claim 10 [*33] actually claims using a "formulation" containing the "complex" to treat the patient. Since the "formulation" is the equilibrium, the Court's definitions of "complex" and "formulation" are fully consistent with the use of these terms in claim 10.

n27 Claim 10 actually recites using the "composition" of claim 1 to treat the patient. However, since the "complex" recited in claim 1 is the only composition of matter recited in claim 1, the term "composition" means a "complex."

For the reasons stated above, the claim language supports the Court's definitions of "complex," "hexamer," and "formulation."

2. The Specification

The above discussion of the meaning of the claim terms is further supported by the specification. The specification supports how the Court interprets the use of "complex," "formulation," and "hexamer" in the claims, including the two meanings of the term "hexamer" dependent on the context in which it is used.

At the outset, the specification uses the term "complex" by itself as a noun, uses [*34] the term "hexamer" by itself as a noun, and uses the phrase "hexamer complex" where "hexamer" is an adjective and "complex" is a noun. Much like the term "hexamer," the specification uses the term "complex" to mean either an equilibrium or a structure, depending on the context in which it is used. n28 In the context of describing the behavior of an equilibrium, and the associated properties of stability and fast action, "complex" is used as shorthand to describe an equilibrium and the term "hexamer" is used as shorthand for the equilibrium where most of the insulin or insulin analog species are aggregated into Zn-hIA structures. n29 When used outside the context of an equilibrium and in the context of individual molecules and their structures, the term "complex" refers to an individual molecular structure and the term "hexamer" refers to a particular type of molecular structure, the Zn-hIA structure. n30 Only one sentence in the specification is ambiguous as to whether "complex" and "hexamer" refer to the equilibrium or the molecular structure. n31 Since claims 1 and 12 only refer to "complex" in the context of individual molecules, the term "complex" is only used in the structural [*35] sense in the claims. Thus, the specification

fully supports the Court's definitions of "complex" and "hexamer" in the claims.

n28 *See* n. 19.

n29 *See* '978 Patent at 2:47-50 ("Brange et al. . . . disclose that when insulin is administered *as a hexamer*. . . the *hexamer* must be sterically more hindered" -- in the Brange et al. reference, the authors are discussing the properties of solutions of human insulin where most of the insulin molecules in the solution are in hexamer structures); *id.* at 62-63 ("The present *formulation* is a zinc-phenolic induced *hexamer complex*" -- this means that most of the insulin analogs in the formulation are in Zn-hIA structures); *id.* at 63-65 ("The rate of absorption for the *hexamer complex* is at least two times that observed with insulin" -- this clause describes the "formulation" and its rapid action); *id.* at 65-66 ("when the *hexamer complex* is formulated, it is equally stable" -- this describes stability of the equilibrium); *id.* at 3:3-5 ("when formulated, this *hexamer complex* retains the fast acting properties" -- this describes the rapid action of the equilibrium); *id.* at 3:30-41 ("FIG. 3 is a graphical representation of Lys<B28>Pro<B29>-human insulin in a *hexamer complex*. The graph is the in vitro dissociation of formulated insulin [degree]; Lys<B28>Pro<B29>-human insulin formulated as a *hexamer complex*. . ." -- this paragraph describes the behavior of equilibrium formulations of hIA so that hexamer complex is used in the equilibrium sense.); *id.* at 4:33-34 ("Both the zinc and phenolic derivative are critical to achieve a *complex* that is stable and capable of rapid dissociation and onset of action" -- this refers to the properties of the equilibrium); *id.* at 5:16-20 ("it is quite surprising that the formulated *hexamer* analog brings a rapid onset of action. Unlike insulin, the formation of an insulin analog *hexamer complex* does not adversely effect the time required to achieve peak serum insulin analog concentration" -- these sentences refer to the properties of the equilibrium state.); *id.* at 5:21-31 ("FIG. 1 demonstrates, in human patients, the mean glucose infusion rate response to a formulation containing monomeric Lys<B28>Pro<B29>-hI (formulated without zinc); a formulated Lys<B28>Pro<B29>-hI *hexamer*; and human regular insulin. The formulated *hexamer complex* retains the rapid action of monomeric Lys<B28>Pro<B29>-hI The absorption rate is significantly more rapid than regular human insulin. Thus, the results in FIG. 1 illustrate: First, *hexamer* Lys<B28>Pro<B29>-hI and monomeric Lys<B28>Pro<B29>-hI have similar rates of absorption; second, both *hexameric* and monomeric Lys<B28>Pro<B29>-hI have faster rates of absorption than insulin" -- this paragraph refers to the rapid action and stability of the equilibrium.); *id.* at 5:32-33 ("The formulation comprising the insulin analog *complex* as *hexamer* is stable" -- this refers to the properties of the equilibrium); *id.* at 5:40 ("Formulated Lys<B28>Pro<B29>-hI, as a *hexamer complex*, exhibits diminished rate of higher molecular weight polymer formation" -- this refers to the equilibrium and its stability.); *id.* at 5:67-6:2 ("Samples of Lys<B28>Pro<B29>-hI as a *hexamer complex* were prepared in an identical fashion except 19.7 [mu] g/ml zinc was added" -- this sentence refers to preparation of a solution that is in equilibrium); *id.* at 6:16-23 ("Degradation is initiated by incubating formulated and unformulated preparations of insulin and monomeric and *hexameric* Lys<B28>Pro<B29>-hI at 30 [degrees] C. The formulated insulin and *hexamer* Lys<B28>Pro<B29>-hI contained: 3.5 mg/ml protein, 16 mg/ml glycerol, 7 mM dibasic sodium phosphate heptahydrate, 1.25 mg/ml m-cresol, 1.09 mg/ml phenol, and 0.0245 mg/ml zinc oxide at a pH of 7.3 to 7.4" -- this refers to the composition of a solution in equilibrium.); *id.* at 6:44-45 ("The in vitro dissociation properties of monomeric Lys<B28>Pro<B29>-hI, Lys<B28>Pro<B29>-hI as a *hexamer complex*, and insulin are probed using static light scattering." This refers to experiments with a solution in equilibrium.); *id.* at 7:12-20 (" FIG. 3 discloses the results of the light scattering study. The in vitro dissociation profile of Lys<B28>Pro<B29>-hI as a *hexamer complex* and insulin are quite different. . . . the formulations are equally stable against chemical degradation, *hexamer* Lys<B28>Pro<B29>-hI has a greater propensity to dissociate than insulin" -- this refers to experiments with equilibrium solutions).

[*36]

n30 *See id.* at Abstract ("The present invention discloses a human insulin analog *complex* and formulations" -- differentiates the structure from the equilibrium); *id.* at 1:61-63 ("The addition of certain metal ions, primarily zinc [to the solution containing insulin], enhance the chemical stability by driving the insulin to form *hexamers*, specifically Zn(II)-T6 conformations" -- First, this language differentiates "hexamers"

from the equilibrium solution. Also, the plural on the word "hexamer" implies that the hexamer is a single structure and that the solution contains multiple hexamers. Finally, the Zn(II)-T6 conformation is a way of describing the structure of an individual molecular structure.); *id.* at 1:64-66 ("phenolics have been shown to specifically bind to the insulin *hexamer* and induce an allosteric conformational change" -- refers to phenolic molecules binding to the insulin hexamer structure.); *id.* at 2:5-6 ("insulin, in the presence of zinc, aggregates to form a well defined *zn-hexamer structure*" -- this teaches that the hexamer complex is a type of structure.); *id.* at 2:13-14 ("the highly stable *Zn-hexamer complex*" -- this refers further to the Zn-hexamer structure.); *id.* at 2:26-28 ("The association that is observed with these analogs is. . .distinct from the predominate, well-defined, Zn-insulin *hexamers.*" -- the use of the plural on "hexamer" indicates that "hexamer" is a single structure); *id.* at 2:31-41 ("In view of the published literature, it is surprising that the present invention affords monomeric insulin analogs in a well defined, stable zinc-phenol *hexamer complex*. This *hexamer complex* is uniquely different from those *complexes* observed with insulin under identical conditions. Insulin *complexes* with zinc and phenol are in a Zn(II)-R[6] conformation. The *hexamer complex* of the present invention is not identical to this conformation. Also quite remarkably, the insulin analog *hexamer complex* has a much greater propensity to dissociate than insulin." -- This paragraph discusses the structure of the hexamer complex of the present invention as distinguished from the R[6] structure observed in the prior art complexes containing insulin. Because the R[6] notation and the term "conformation" refer to structure of a single hexamer complex of insulin, *see* Tr. at 197:18-203:23; 209:13-210:4, the patent teaches that "complex" and "hexamer complex" refer to a single structure); *id.* at 2:45-46 ("the obvious route to creating a fast-acting insulin is to prevent dimer or *hexamer* formation" -- this indicates that the goal is to avoid the formation of individual hexamer structures in the equilibrium.); *id.* at 2:58-59 ("efforts to chemically stabilize the monomeric insulin analog with zinc by forming a well defined, *hexamer complex*," referring to forming a molecular structure.); *id.* at 3:11-16 ("This invention provides a human insulin analog *complex*, which comprises: six molecules of a human insulin analog, two zinc ions, and at lease three molecules of a phenolic derivative selected from the group consisting of m-cresol, phenol, or a mixture of m-cresol and phenol; such that the analog *complex is a hexamer.*" -- This sentence defines the "complex" as a molecular structure by defining it in terms of the molecules that are part of the structure. It defines "hexamer" as a particular type of molecular structure.); *id.* at 3:16-17 ("The invention further provides parenteral formulations comprising the *hexamer complex*" -- differentiating between the formulation, i.e., the equilibrium, and the hexamer complex in the equilibrium); *id.* at 3:45-46 ("the invention provides a monomeric human insulin analog *complex* as a *hexamer*" -- refers to a single molecular structure.); *id.* at 4:30-33 ("The insulin analogs of the present invention *complex* with zinc ions and a phenolic derivative to form a stable, *hexamer conformation*" -- here, the term "hexamer" is used to describe the conformation, which generally refers to a molecular structure.); *id.* at 4:60-61 ("The *hexamer complex* may be *formulated* into stable, rapid acting parenteral *formulations*" -- differentiates the molecular structure from formulating it into an equilibrium.); *id.* at 4:67-5:1 ("two zinc ions are bound to each *hexamer*" -- in this phrase "each hexamer" refers to each of the individual molecular structures in the equilibrium.); *id.* at 5:1-3 ("the *hexamer complex* binds as many as seven phenolics. Generally, when formulated, six phenolics are bound to the *hexamer.*" -- Here, "complex" and "hexamer" refer to the individual molecular structure because it lists the number of molecules bound to the hexamer structure.); *id.* at 7:17-18 ("both preparations contain *hexameric* association states" -- the use of the plural indicates that the hexameric association states refer to individual molecular structures in the solution).

[*37]

n31 *Id.* at 4:34-35 ("The *hexamer complex* consists of two zinc ions *per hexamer* of human insulin analog and at least three molecules of a phenolic derivative selected from the group consisting of m-cresol, phenol, or a mixture of m-cresol and phenol.") One could argue that "hexamer complex" refers to the equilibrium and that the second instance of "hexamer" refers to the structure because the "hexamer complex" is composed of "two zinc ions *per* hexamer of human insulin analog," implying that the "complex" contains multiple "hexamers." However, the sentence also states that the "hexamer complex" is composed of "at least three molecules of phenolic derivative," but not *per* hexamer, implying that

there are only three molecules of phenolic in the complex and that the complex refers to the structure. Given the ambiguities in the drafting of this sentence and the clear drafting throughout the rest of the specification, the language of this sentence will be ignored for purposes of claim construction.

The specification also supports the Court's definition of "formulation" as the equilibrium. [*38] When the specification uses the terms "formulation" or "formulated" it refers to the equilibrium or the rapid action and stability of the equilibrium. n32 Therefore, as defined above, the "formulation" refers to the equilibrium state.

n32 *See id.* at Abstract ("invention discloses a human insulin analog hexamer complex and *formulations*" -- differentiates between structure and the equilibrium "formulation"); *id.* at Abstract ("*formulation* [not complex or hexamer] provides rapid onset of action" -- discusses the rapid action of the equilibrium); *id.* at 1:14-15 ("various *formulations* with different time-actions have been developed"); *id.* at 1:28-31 ("Recently, considerable effort has been devoted to create insulin *formulations* and insulin analog *formulations* that alter the kinetics of the subcutaneous absorption process" -- discusses the rapid action properties of the equilibrium.); *id.* at 1:24-32 ("all commercial pharmaceutical *formulations* of insulin contain insulin in the self associated state and predominantly in zinc-hexamer form." -- this sentence states that "formulations" are equilibria which contain the free constituents, insulin and zinc, and the hexamer complexes.); *id.* at 2:65-67 ("when the hexamer complex is *formulated*, it is equally stable" -- discusses stability of equilibrium) *id.* at 3:2-5 ("when *formulated* this hexamer complex retains the fast acting properties" -- discusses stability of equilibrium); *id.* at 3:15-16 ("the invention further comprises parenteral *formulations* of the hexamer complex" -- the formulation is the equilibrium that contains the complexes); *id.* at 3:36-41 ("*formulated* samples contained [concentrations of solutions]" -- the "formulation" is the equilibrium state because it is defined in terms of solution concentrations); *id.* at 3:30-41 ("FIG. 3 is a graphical representation of Lys<B28>Pro<B29>-human insulin in a hexamer complex. The graph is the in vitro dissociation of *formulated* insulin [degree]; Lys<B28>Pro<B29>-human insulin *formulated* as a hexamer complex. . ." -- This paragraph describes the behavior of equilibrium formulations of hIA.); *id.* at 4:60-61 ("the hexamer complex may be *formulated* into stable, rapid, acting parenteral *formulations*," discussing the equilibrium); *id.* at 5:3 ("when *formulated*, six phenolics are bound to the hexamer" -- teaches that the formulation is the equilibrium solution which contains multiple hexamers); *id.* at 4:67-5:1 ("in the *formulation* . . . two zinc ions are bound to each hexamer" -- teaches that the formulation is the equilibrium solution which contains multiple hexamers); *id.* at 5:8-13 ("An isotonicity agent, preferably glycerin, may be added to the formulation. The concentration of the isotonicity agent is in the range known in the art for insulin formulations, preferably about 16 mg/ml. The pH of the formulation may be buffered with a physiologically tolerated buffer, preferably a phosphate buffer, like sodium phosphate" -- this paragraph discusses other ingredients that can be added to the equilibrium.); *id.* at 5:17-18 ("*formulated* hexamer brings on rapid onset of action" -- discusses the rapid action of the equilibrium); *id.* at 5:40-44 ("*formulated* Lys<B28>Pro<B29>-hI, as a hexamer complex, exhibits a diminished rate of higher molecular weight polymer formation" -- refers to the rapid action of the equilibrium); *id.* at 5:33-34 ("the *formulation* comprising the insulin analog complex is stable"); *id.* at 6:16-23 ("Degradation is initiated by incubating *formulated* and unformulated preparations of insulin and monomeric and hexameric Lys<B28>Pro<B29>-hI at 30 [degrees] C. The *formulated* insulin and hexamer Lys<B28>Pro<B29>-hI contained: 3.5 mg/ml protein, 16 mg/ml glycerol, 7 mM dibasic sodium phosphate heptahydrate, 1.25 mg/ml m-cresol, 1.09 mg/ml phenol, and 0.0245 mg/ml zinc oxide at a pH of 7.3 to 7.4." -- This refers to the composition of a solution in equilibrium.); *id.* at 7:12-20 ("FIG. 3 discloses the results of the light scattering study.. . . the *formulations* are equally stable against chemical degradation, hexamer Lys<B28>Pro<B29>-hI has a greater propensity to dissociate than insulin" -- this refers to experiments with equilibrium solutions.).

The term "formulated" refers to a "formulation" where most of the species are in hexamer structures, while the term "unformulated" refers to a "formulation" where most of the species are not in hexamer structures. *See id.* at 30-41 ("FIG. 3 is a graphical representation of the dissociation of Lys<B28>Pro<B29>-human insulin in a hexamer complex. The graph is the in vitro dissociation of *formulated* insulin; Lys<B28 Pro<B29>-hI *formulated* as a hexamer complex;

> *unformulated* insulin; and monomeric Lys<B28>Pro<B29>-hI monitored by static light scattering at 488 nm at a 90 [degrees] angle. The *formulated* samples contained 0.5 mol Zn per mol protein, 1.25 mg/ml m-cresol and 1.09 mg/ml phenol, 7 mM sodium phosphate and 16 mg/ml glycerol. The *unformulated* and monomeric samples contained no additional excipients." -- This paragraph illustrates how the words formulated and unformulated are used to refer to hexameric and monomeric solutions, respectively); *id.* at 5:36-40 ("*Unformulated* human insulin undergoes a slower rate of polymer formation of 0.61% per week. Upon formulation, however, the rate of high molecular weight polymer formation is reduced to 0.095% per week for insulin"); *id.* at 5:17-18 ("*formulated* hexamer brings on rapid onset of action"); *id.* at 5:40-44 ("*formulated* Lys<B28>Pro<B29>-hI, as a hexamer complex, exhibits a diminished rate of higher molecular weight polymer formation"); *id.* at 5:62-6:2 ("*Unformulated* samples of insulin and Lys<B28>Pro<B29> -hI were prepared at 3.5 mg/ml in 7 mM sodium phosphate, and with or without 1.25 mg/ml m-cresol, 1.09 mg/ml phenol and 16 mg/ml glycerol, depending on the experiment performed. Samples of Lys<B28>Pro<B29>-hI as a hexamer complex were prepared in an identical fashion except 19.7 mu g/ml zinc was added."); *id.* at 6:16-23 ("Degradation is initiated by incubating *formulated* and *unformulated* preparations of insulin and monomeric and hexameric Lys<B28>Pro<B29>-hI at 30 [degrees] C. The *formulated* insulin and hexamer Lys<B28>Pro<B29>-hI contained: 3.5 mg/ml protein, 16 mg/ml glycerol, 7 mM dibasic sodium phosphate heptahydrate, 1.25 mg/ml m-cresol, 1.09 mg/ml phenol, and 0.0245 mg/ml zinc oxide at a pH of 7.3 to 7.4."); *id.* at 6:48-50 ("Three *formulated* and *unformulated* protein stock solutions are prepared as described except that the unformulated protein stock solutions did not contain zinc, glycerol, or preservatives [i.e., they do not form hexamers]").

[*39]

Thus, the specification validates the Court's definitions of "complex," "hexamer," and "formulation."

3. The Prosecution History

The next step is to turn to the prosecution history to help understand the terms in the claims. *See Multiform Desiccants*, 133 F.3d at 1478. The prosecution history provides support for the Court's definitions of "complex," "hexamer," and "formulation."

First, the arguments in the prosecution history support that the terms "complex" and "hexamer" have different meanings in different contexts. In the context of describing the behavior of a "formulation," or equilibrium, and the associated properties of stability and fast action, the terms "complex" and "hexamer" are used as shorthand for the equilibrium where most of the insulin or insulin analog species are aggregated into Zn-hIA structures. n33 When used outside the context of an equilibrium and in the context of individual molecules, the terms "complex," "hexamer," and "hexamer complex" refer to the Zn-hIA structure. n34 Therefore, the prosecution history supports the two definitions of "complex" and "hexamer." Second, the arguments in the prosecution history support the definition [*40] of "formulation" as an equilibrium. n35 The prosecution history, like the claim language and specification, confirms the Court's definitions of "complex," "hexamer," and "formulation."

n33 *See* Amendment and Remarks of March 14, 1995, Novo Ex. D at A-370 ("when phenol or m-cresol is added to a zinc solution of a monomeric analog, the monomeric analog forms a well ordered, hexamer association state" -- refers to the equilibrium solution.); *id.* ("the *hexamer* association state retains a rapid profile of action" -- refers to the properties of the equilibrium.").

The following passage also illustrates how the word "hexamer" is used in the equilibrium sense, to distinguish the prior art based on the predominance of hexamers structures in the equilibrium and the rapid time action of this equilibrium:

> Therefore, in view of Brems et al., one skilled in the art would predict that a monomeric analog would remain predominantly monomeric and any association monomeric and any association observed would be to a mixture of aggregates. Thus Brems et al. suggest that the present invention would fail -- the zinc-phenolic induced association of monomeric analogs into a hexamer is most unexpected. The present invention demonstrates that the claimed analogs form a well ordered, zinc/phenol hexamer. . . Most significantly, the association of the monomeric analog into a hexamer does not change the time action.

Id. at A-375.

[*41]

n34 *See id.* at A-370 ("The addition of zinc. . . does not induce aggregation to well, defined *hexamers* of the analog" -- the plural of hexamers indicates that these are the structures in the equilibrium); *id.* ("the present invention claims the *hexamer* analog *complex*, formulations, and methods" -- distinguishes the molecular structure from the equilibrium.); *id.* at A-372 ("Clearly, Wollmer et al. do not disclose an *analog* containing 2 Zn ions and at least 3 phenol derivative in a *hexamer* conformation." -- This sentence defines "complex" as a structure by referring to the number of molecules in the complex, and defines "hexamer" as a structure by referring to its conformation.); *id.* at A-373 ("the present monomeric analogs *complexes* and formulations" -- distinguishes the structure from the equilibrium.); *id.* at A-374 ("Wollmer et al. study. . . *structural* transformations of insulin *hexamers*. . . [and] the 2 Zn to 4 Zn transition of insulin is a property of *hexamers*" -- refers to structures); *id.* ("Wollmer et al. do not disclose des(B26-B30)-insulin in a *hexamer* conformation" -- refers to the structure); *id.* ("because the CD-spectral effects observed with des(B26-30)-insulin are different and opposite than those observed with insulin *hexamers*, one of ordinary skill in the art would conclude that the *hexameric complex* could not be formed with the monomeric insulin analog." -- In this section, Lilly is referring to the structure of the hexamers.).

Moreover, the following passage illustrates how Lilly attempted to distinguish the structure of the claimed hexamer complex from prior art hexamer complex:

> Insulin in the presence of zinc is in a T[6] hexamer association state. When phenol is added, the conformation changes to a R[6] hexamer association. Brems et al. report that monomeric analogs do not form a hexameric T[6] association state with zinc. In view of Brems et al., it logically follows that one of ordinary skill in the art would predict that the monomeric analog would not change its conformation to an R[6]-like hexameric association state with zinc and phenol. . . The present invention demonstrates that the claimed analogs form a well ordered, zinc/phenol hexamer. However, this association state is not analogous to the R[6] association state observed with insulin.

Id. at A-375.

[*42]

n35 *See id.* at A-370 ("the present invention claims the hexamer analog complex, formulations, and methods" -- distinguishes the equilibrium from the molecular structures.); *id.* at A-373, A-375 ("The novelty of the present invention lies in the zinc-phenolic induced association and the subsequent rapid time action of the *formulation*" -- refers to the rapid time action of the equilibrium.); Office Action of Jan. 27, 1995, Novo Ex. D at A-353 ("*formulations* are disclosed which. . . are intended to provide rapid onset of action combined with improved stability." -- Lilly did not dispute this use of the term "formulation" by the Examiner).

4. Extrinsic Evidence

Both parties invite the Court to examine reams of extrinsic evidence, including dictionary definitions, prior art, expert testimony, and inventor testimony. Because the definitions of "complex," hexamer," and "formulation" are clear from the intrinsic evidence of the patent, it is not necessary, and indeed improper, to examine the extrinsic evidence proffered by the parties. *See Pitney Bowes*, 182 F.3d at 1309. [*43] Therefore, the Court declines the invitation to examine the extrinsic evidence.

However, in the interests of judicial caution, in light of recent Federal Circuit law, the Court notes that the dictionary definitions are in accord with the Court's definitions. n36 First, the dictionaries validate that "complex" means a molecular structure. n37 The dictionary definitions do not illuminate the meaning of the term "hexamer." n38 The parties submitted no dictionary definitions of "formulation." Therefore, the dictionary definitions do not contradict the Court's definitions of "complex," "hexamer," and "formulation."

n36 [HN12] Prevailing Federal Circuit law has always held that dictionaries are extrinsic evidence. *See, e.g., Vitronics*, 90 F.3d at 1584-85. However, in a recent non-precedential decision, a diminished panel of the Federal Circuit held that "dictionary definitions are considered to be intrinsic evidence." *Antonious v. Spalding & Evenflo Cos., Inc.*, 1999 U.S. App. LEXIS 22984, 1999 WL 777450, *3 (Fed. Cir. 1999). Moreover, in several other cases, the court seems to have employed a dictionary as part of its intrinsic analysis of the plain meaning of the claim language. *See, e.g., Karlin Tech., Inc. v. Surgical Dynamics, Inc.*, 177 F.3d 968, 971 (Fed. Cir. 1999) (using dictionary definitions as part of the intrinsic evidence analysis of the claim language); *Desper Products, Inc. v. QSound Labs, Inc.*, 157 F.3d 1325, 1333 (Fed. Cir. 1998) (same). Nonetheless, absent explicit precedential authority to the contrary, this Court will consider dictionaries as extrinsic evidence. Whether the dictionaries are intrinsic or extrinsic evidence does not affect the outcome of claim construction in this case.

[*44]

n37 *See* Oxford Dictionary of Biochemistry & Molecular Biology -- (2d ed. 1989) ("an aggregate of two or more molecules, particularly macromolecules, held together by non-covalent forces in a definable structural relation and as a result of particular interactions"); Grant & Hackh's Chemical Dictionary (1987) ("ion or compound, which in solution dissociates reversibly into its component parts" or "ion or compound which is sufficiently stable to retain its identity in solution"); Merriam-Webster's New Collegiate Dictionary (1998) ("a chemical association of two or more species (as ions or molecules) joined usu. by weak electrostatic bonds rather than covalent bonds"); Merriam-Webster's New Collegiate Dictionary (1993) (1. "a whole made up of complicated or interrelated parts" -- referring in general to a type of structure; 2. "a complex substance (as a coordination complex) in which the constituents are more intimately associated than in a simple mixture"); Webster's Third New Int'l Dictionary (1981) ("a conjunction of varied contributing or interacting factors, elements, or qualities: as a complex substance (as a coordination compound, an ion containing several atoms, or an adsorption compound -- usu. distinguished from mixture"); Random House Dictionary (1987) (Lilly Ex. 26) ("10. a compound in which independently existing molecules or ions of a non-metal form coordinate bonds with a metal atom or ion; 11. an entity composed of molecules in which the constituents maintain much of their chemical identity: receptor-hormone complex, enzyme substrate complex").

[*45]

n38 Only the roots of the word "hexamer" actually appear in the dictionary. *See* Webster's New Collegiate Dictionary (1989) ("hexa-" = "six; containing six atoms, groups, or equivalents"; "mer" = "member of a specified class (*monomer*)"); Random House Dictionary (1987) (Lilly Ex. 26) ("hexa-" = "a combining form meaning six"; "-mer" = "a combining form meaning member of a particular group").

B. "pharmaceutical"

Lilly maintains "pharmaceutical" does not have a separate meaning outside the context of "pharmaceutical formulation." Lilly then reasons that "pharmaceutical" means "an aqueous solution formulated to be of appropriate safety and efficacy for treatment of patients." D.I. 156 at 2. Like Lilly, Novo does not define "pharmaceutical" independently of "formulation." However, Novo urges a different definition, namely, "pharmaceutical" means "containing a medicinal drug or a biologically active agent and. . . suitable for administration to an animal." D.I. 154 at 33. The Court holds "pharmaceutical" means "containing a medicinal drug" where "medicinal drug" means "a substance [*46] or preparation used in treating disease." n39

n39 Although the Court's definition of "pharmaceutical" is not identical to the definitions proffered by the parties, this definition is more accurate. *See Exxon Chemical Patents*, 64 F.3d 1553 at 1556 ("the judge's task is not to decide which of the adversaries is correct. Instead the judge must independently. . . declare the meaning of the claims").

The intrinsic evidence does not provide a clear definition of the term "pharmaceutical." First, the meaning of "pharmaceutical" is not immediately apparent from the text of the claims. Second, the specification does not define the term "pharmaceutical" and uses the term only once, without defining it:

> Because all commercial *pharmaceutical* formulations of insulin contain insulin in the self-associated state and predominately in the zinc-hexamer form, it is believed that the rate-limiting step for the absorption of insulin from the subcutaneous injection depot to the bloodstream is the dissociation [*47] of the self-aggregated insulin hexamer.

'978 Patent at 1:33-39. This discussion sheds no light on the meaning of "pharmaceutical." Finally, the prosecution history provides no guidance as to the meaning of "pharmaceutical." *See* Novo Ex. D.

With the intrinsic evidence not being helpful, the Court turns to extrinsic evidence. Various dictionary definitions support the Court's definition of "pharmaceutical" as "containing a medicinal drug." n40 Moreover, the dictionary definitions support the Court's definition of "medicinal drug" as "a substance or preparation used in treating disease." n41

> n40 *See* Oxford Dictionary of Biochemistry and Molecular Biology 495 (1997) ("of or pertaining to drugs or pharmacy" or "any medicinal substance, mixture or formulation"); Dictionary of Biochemistry and Molecular Biology 355 (2d ed. 1989) ("a drug" or "of, or pertaining to pharmacy" where "pharmacy" means "the branch of pharmacology that deals with the origin, the composition, the preparation, and the dispensing of drugs"); Merriam-Webster's Collegiate Dictionary 870 (10th ed. 1998) ("of, relating to, or engaged in pharmacy" where "pharmacy" means "the art, practice, or profession, of preparing, preserving, compounding, and dispensing medical drugs"); Merriam-Webster's New Collegiate Dictionary 852 (1981) ("of, relating to pharmacy" where "pharmacy" means "the art or practice of preparing, preserving, compounding, and dispensing drugs"); Grant & Hackl's Chem. Dictionary 437 (1987) ("pertaining to drugs; the analysis of drugs and isolation of their active constituents"); Hawley's Condensed Chem. Dictionary 891 (1993) ("a broad term that includes not only all types of drugs and medicinal and curative products but also ancillary products such as tonics, dietary supplements, vitamins, deodorants, and the like"); Webster's Third New Int'l Dictionary 1694 (1981) ("of or relating to pharmacy" where "pharmacy" means "1. the administering of drugs: treatment by drugs; 2. the art or practice of preparing, preserving, compounding, and dispensing drugs").

[*48]

> n41 *See* Webster's Third New Int'l Dictionary 695, 1403 ("drug" means "a substance used as a medicine" and "medicine" means "a substance or preparation used in treating disease").

The Court's definition of "pharmaceutical" comports with the idea behind the patent, to create an insulin analog formulation that is useful as a drug to treat diabetes. *See* '978 Patent at 1:11-60. Indeed, claim 10 recites a method of using a "pharmaceutical formulation" of the complex for "treating a patient suffering from diabetes mellitus." The specification defines "treating" as:

> the management and care of a patient for the purpose of combating the disease, condition, or disorder and includes the administration of a compound of present invention to prevent the onset of the symptoms or complications, alleviating the symptoms or complications, or eliminating the disease, condition, or disorder.

'978 Patent at 4:9-15. It follows that the Court's definition of "pharmaceutical" is consistent with the invention disclosed in the specification.

Lilly maintains that the term "pharmaceutical" also means [*49] that the formulation is safe and effective for treatment of diabetes. Lilly argues that "safe" means that the formulation is chemically stable and has a low rate of polymer formation. *See* D.I. 156 at 15 (citing '978 Patent at 1:57-60; 2:62; 3:5-7; 4:60-61; 5:32-34). Lilly also argues that "effective" means that the hexameric hIA retains the rapid action of monomeric hIA. *See id.* However, the specification does not state anywhere that the term "pharmaceutical" means safe and effective, as Lilly has defined the terms. Moreover, a pharmaceutical can be a medicinal drug, used in the treatment of disease, without necessarily being safe or effective. *See, e.g., In re Bendectin Litigation*, 857 F.2d 290, 321 (6th Cir. 1988) (referring to the teratogenic properties of thalidomide, a medicinal drug).

Lilly also relies on the Food, Drug and Cosmetic Act definition of "drug" and criteria for "drug" approval for support of its definition. *See* 21 U.S.C. § 321(g)(1) (1999) ("drug" means "a substance intended for use in

the diagnosis, cure, mitigation, or prevention of disease"); *id.* at § 355(b)(1)(A) (the FDA will only approve a "drug" if [*50] it is both safe and effective). However, reliance on this definition is inappropriate because the FDA, not the Patent and Trademark Office, is responsible for determining whether drugs are safe and effective and because drugs not approved by the FDA are still patentable. *See Application of Anthony*, 56 C.C.P.A. 1443, 414 F.2d 1383, 1395 (C.C.P.A. 1969).

Novo's interpretation of "pharmaceutical" is also too limiting because it includes the possibility that the formulation is "a biologically active agent" and that the formulation is "suitable for administration to an animal." A formulation containing only one hexamer complex of hIA would suffice as a "biologically active agent" but would not be "pharmaceutical" because it alone could not be used to treat a disease. Also, there is no limitation in the claims, specification, or prosecution history that a "pharmaceutical" formulation must be "suitable for administration to an animal." Instead, the touchstone is whether the formulation is "a substance or preparation used in treating disease."

For these reasons the Court declines to adopt the respective claim constructions proffered by the litigants, and instead holds that [*51] "pharmaceutical" means "containing a medicinal drug" where "medicinal drug" means "a substance or preparation used in treating disease."

C. "comprises. . . two zinc ions"

Lilly urges that, although "two zinc ions" means "two ions of zinc," D.I. 156 at 3, "comprises" denotes open claim language and "opens the claim to the inclusion of additional elements or materials," including more than two zinc ions per hexamer. D.I. 156 at 2, 28-29. Novo argues that "comprises" means "that the claimed human insulin analog complex can have other components in the complex, in addition to the named components in the named amounts, but can not have the named components in different amounts," D.I. 154 at 27, and that "two zinc ions" means that "each claimed complex has two and only two zinc ions." D.I. 154 at 28. Boiled down, this particular dispute centers on whether "comprises. . . two zinc ions" means that each hexamer complex can have at least two zinc ions (Lilly) or only two zinc ions (Novo).

[HN13] When used as a transition, as in claim 1, the term "comprises" means that the claim is open ended, so that it may include elements other than those explicitly recited in the claim. *See, e.g.*, [*52] *Carl Zeiss Stiftung v. Renishaw*, 945 F.2d 1173, 1178 (Fed. Cir. 1991). The litigants agree that the hexamer complex of claim 1 could also include calcium or acetate ions in addition to the hIA, zinc, and phenolics recited in claim 1. *See* Tr. at 241:17-23.

However, in claim 1, the use of the term "comprising" does not allow more than two zinc ions per hexamer complex because claim 1 precedes "three phenolics" with the phrase "at least" but does not precede "two zinc ions" with "at least." [HN14] The expression of a limitation in one element of a claim implies the exclusion of that term in other elements of the claim. *Cf. Modine Mfg. Co. v. U.S. Int'l Trade Comm'n*, 75 F.3d 1545, 1551 (Fed. Cir. 1996). Moreover, each term in each claim must be given meaning. *See Warner-Jenkinson Co.*, 520 U.S. 17 at 29, 137 L. Ed. 2d 146, 117 S. Ct. 1040. In order to give meaning to the choice to use the term "at least" to modify only "three phenolics," claim 1 must mean that a hexamer complex can contain more than three phenolics but not more than two zinc ions per hexamer. n42

n42 Eli Lilly may argue that reading "comprises. . . two zinc ions" to mean that there must be exactly two zinc ions renders meaningless claim 12 which is identical to claim 1 except that it uses the closed language "consisting of. . . two zinc ions." However, claims 1 and 12 can be differentiated even though both are directed to the structure and not the equilibrium. Although both require exactly two zinc ions, claim 1 allows inclusion of other species in the complex, while claim 12 does not allow inclusion of any species other than the ones recited in the claim.

[*53]

The Court holds that "comprising. . . two zinc ions" means that the claimed human insulin analog complex may have other components in the complex, in addition to the named components, but must have the named components, including the two zinc ions, in the specified amounts.

D. "consisting of"

Lilly argues that "consisting of" indicates "closed claim language. It closes the claim to the inclusion of materials other than those recited, *except for components ordinarily associated therewith*." D.I. 156 at 3 (emphasis added) (citing *Sakano v. Rutemiller*, 158 U.S.P.Q. 47, 51 (Bd. Pat. Interf. 1968); *Ex Parte Davis*, 80 U.S.P.Q. 448, 450 (Bd. App. 1948)). Novo urges that "consisting of" means that "the claim is closed to additional components . . . [and] the claimed complex can include *only* the named components in the named amounts." D.I. 154 at 35 (citing *Schering v. Amgen Inc.*, 18 F. Supp. 2d 372, 382 (D. Del. 1998)). n43

n43 Novo also cites *PPG Industries v. Guardian Industres*, 156 F.3d 1351 (Fed. Cir. 1998). However, that case construes the meaning of "consisting essentially of," not "consisting of" and, therefore, is not applicable.

[*54]

Both parties are partially correct. *Sakano* and *Davis*, both chemical cases, hold that "consisting of" closes the claim "except for *impurities* ordinarily associated therewith." *See Sakano*, 158 U.S.P.Q. at 51; *Davis*, 80 U.S.P.Q. at 450 (emphasis added). Therefore, [HN15] in the context of chemical patents, "consisting of" indicates closed claim language and closes the claim to the inclusion of unrecited elements, except for impurities ordinarily associated therewith.

E. "wherein the human insulin analog is. . . des (B27)-human insulin" and "the T[6] limitation"; and "hexamer" and "the R[6] limitation"

Novo argues that the language "wherein the human insulin analog is. . .des(B27)-human insulin" includes a limitation that the listed hIA's do not form T[6] hexamer structures in the presence of zinc alone ("the T[6] limitation"). Novo also asserts that the term "hexamer" includes a limitation that the Zn-phenolic-hIA hexamer has a conformation different from the R[6] conformation of the Zn-phenolic-hI hexamer ("the R[6] limitation").

1. "wherein the human insulin analog is. . . des (B27)-human insulin" and "the T[6] limitation" [*55]

Lilly argues that "wherein the human insulin analog is. . ." means that "the human insulin analog is one of the twelve recited analogs." D.I. 156 at 3. Novo argues that "wherein the human insulin analog is. . ." means that "the analog in the hexamer complex *does not form a hexameric T[6]-like association state with zinc* and is one of the twelve analogs spelled out in the claim." n44 D.I. 154 at 32. At bottom, the litigant's disagreement centers on whether this claim language includes a limitation that the twelve hIA's do not form a T[6]-like association state with zinc alone ("the T[6] limitation"). n45 The Court agrees with Lilly and holds that this language does not include the T[6] limitation, but merely recites the twelve different types of insulin analogs that can form a hexamer complex.

n44 Both parties agree that the twelve recited analogs in the claim are:

Asp<B28> human insulin
Lys<B28> human insulin
Leu<B28> human insulin
Val<B28> human insulin
Ala<B28> human insulin
Asp<B28> Pro<B29> human insulin
Lys<B28> Pro<B29> human insulin
Leu<B28> Pro<B29> human insulin
Val<B28> Pro<B29> human insulin
Ala<B28> Pro<B29> human insulin
des(B28-B30) human insulin
des(B27) human insulin.

[*56]

n45 Prior art teaches that hIA's generally do not form a stable T[6] hexamer complex with zinc alone. *See* Brems et al., Altering the Association Properties of Insulin by Amino Acid Replacement, 5 Protein Engineering 527, 529-33 (1992). The '978 patent also recognizes this fact. *See* '978 Patent at 2:13-15. However, at oral argument, Novo indicated that at least one of the analogs in the list of twelve does form stable T[6]-like association states in the presence of zinc alone. *See* Tr. at 366:21-367:11. Whatever the fact may be, it plays no part in resolution of the *Markman* issues before the Court because, *inter alia*, it lacks record support.

First, the claim language does not explicitly support this limitation. Indeed the claim language is extremely clear. It simply recites a list of twelve analogs which can comprise the insulin analog complex. There is no mention that these analogs do not form T[6] association states in the presence of zinc alone.

Further, the specification explicitly defines "human insulin analog" as "human insulin wherein:

Pro at position [*57] B28 is substituted with Asp, Lys, Leu, Val, or Ala; and Lys at position B29 is Lysine or substituted with Proline;
des(B28-B30); or
des(B27)."

'978 Patent at 3:47-55. In short, the patentee acted as his own lexicographer in defining the meaning of the claim term "human insulin analog."

Even though the claim language and the specification are clear, Novo nonetheless attempts to add this additional T[6] limitation to the claim. It first searches the specification for this limitation. Novo cites language in the specification which states that "any aggregation between zinc and the insulin analog is distinct from that observed with insulin," '978 Patent at 2:7-9; that "Asp-Pro-hI, AlaPro-hI, and LysPro-hI show little or no Zn-induced association and that Pro-insulin, Lys-insulin, Asp-insulin, and Ala-insulin demonstrate Zn-induced association, but less than Zn-insulin," '978 Patent at 2:18-23; and, that "insulin analogs do not form the Zn(II)-T[6] conformation in a manner analogous to insulin," '978 Patent at 2:29-30.

Novo ignores the principle that [HN16] "interpreting what is meant by a word in a claim is not to be confused with adding an extraneous limitation appearing in the [*58] specification, which is improper." *Intervet Am., Inc. v. Kee-vet Laboratories, Inc.*, 887 F.2d 1050, 1053 (Fed. Cir. 1989). In this case, Novo is attempting to import extraneous language discussing the prior art into the claim language. Since the patentee has acted as his own lexicographer in clearly defining this language, the importation of the T[6] limitation is improper.

Novo further relies on the prosecution history for support of its proposed T[6] limitation. This claim language was added in an amendment in response to an Office Action rejecting the claims based on a lack of enabling disclosure under 35 U.S.C. § 112 (first paragraph) and based on prior art under 35 U.S.C. § § 102(b), 103(a). Novo argues that the added language requires that the twelve hIA's "not form a hexameric T[6]-like association state with zinc" because of the attorney comments related to the § 103(a) rejection:

> Insulin in the presence of zinc is in a T[6] hexamer association state. . . Brems et al. report that monomeric analogs do not form a hexameric T[6] association state with zinc. In view of Brems et al., it logically follows [*59] that one of ordinary skill in the art would predict that the monomeric analog would not change its conformation to an R[6]-like hexameric association state with zinc and phenol.

Plaintiffs Ex. D, A-375.

[HN17] The prosecution history can only be used to understand the meaning of the terms in the claims, not to "enlarge, diminish or vary the limitations in the claims." *Armament Systems and Procedures, Inc. v. Monadnock Lifetime Products, Inc.*, 168 F.3d 1319, 1998 WL 537746 at *3 (Fed. Cir. 1998). Novo is attempting to import a discussion of the prior art in the prosecution history into the clearly defined terms in the claims. n46 This is not permissible. It follows this claim language does not include the T[6] limitation.

> n46 "Use of the prosecution history to *interpret* claim language is distinct from prosecution history *estoppel*, which is a limitation on the doctrine of equivalents." Chisum on Patents at § 18.03[d][2]; *see also Amhil Enterprises*, 81 F.3d at 1559. Accordingly, the Court does not reach the question of prosecution history estoppel.

[*60]

Accordingly, "wherein the human insulin analog is. . .des (B27)-human insulin" means that "the human insulin analog is one of the twelve recited analogs" and does not include the R[6] limitation.

2. "hexamer" and "the R[6] limitation"

Novo argues that the term "hexamer" includes a limitation that the hexamer structure "is not analogous to the R[6] hexamer of human insulin" ("the R[6] limitation"). D.I. 154 at 28. Lilly answers that the term "hexamer" contains no such limitation. D.I. 156 at 2. The Court holds that the definition of "hexamer" does not include the R[6] limitation.

As discussed in Part IV.A, *supra*, the plain language of the claim does not include the R[6] limitation. The specification also includes no such limitation. Novo argues that the limitation is found in the prosecution history in attorney comments related to the § 103(a) rejection:

> In view of Brems et al., it logically follows that one of ordinary skill in the art would predict that the monomeric analog would not change its conformation to an R[6]-like hexameric association state with zinc and phenol. . . The present invention demonstrates that the claimed analogs form a well [*61] ordered, zinc/phenol hexamer. However, this association state is not analogous to the R[6] association state observed with insulin.

Plaintiffs Ex. D, A-375. Novo argues that "hexamer" must refer to a structure not analogous to the R[6] association state because the patentee explicitly disclaimed this structure as part of the invention in order to persuade the Examiner that the invention was not an obvious improvement over the prior art.

Novo's argument fails because, as discussed in Part IV.A, *supra*, the claim language and the specification define the term "hexamer" and do not include any R[6] limitation. As previously rehearsed, the prosecution history can only be used to understand the meaning of the terms in the claims, not to "enlarge, diminish or vary the limitations in the claims." *Armament Systems and Procedures, Inc. v. Monadnock Lifetime Products, Inc.*, 168 F.3d 1319, 1998 WL 537746 at *3 (Fed. Cir. 1998). Like its efforts with respect to the T[6] limitation, Novo is attempting to import a discussion of the prior art in the prosecution history into the clearly defined terms in the claims. n47 The R[6] limitation similarly fails. It is [*62] held this claim language does not include the R[6] limitation.

n47 *See* n.46, *supra*.

F. "parenteral," "administering," and "patient"

Lilly urges that "parenteral" means "for subcutaneous injection into a patient." D.I. 156 at 3. Novo counters that "parenteral" means "taken into the body or administered in a manner other than through the digestive tract (*e.g.*, not by mouth or through the alimentary canal)." D.I. 154 at 33. The court holds that Novo's interpretation of "parenteral" is correct.

Lilly maintains that "administering" means "subcutaneous injection." D.I. 156 at 2. Novo argues that "administer" means "to apply as a remedy." D.I. 154 at 34. The court holds that Novo's interpretation of this term is correct.

Lilly argues that "patient" means "a human being." D.I. 156 at 2. Novo replies that "patient" means "an animal, including a human being." D.I. 154 at 34. This Court holds that "patient" means an animal, including a human being, awaiting or under medical treatment.

The meanings [*63] of "parenteral," "administering," and "patient" are not immediately apparent from reading the plain language of the claim. n48 Moreover, the specification and the prosecution history fail to explicitly define these terms as they have done for terms such as "isotonicity agent" and "treating." *See* '978 Patent at 4:9-20. Therefore, it is appropriate to turn to extrinsic sources of evidence.

n48 Novo argues that the doctrine of claim differentiation precludes defining the term "administering" to mean "subcutaneous injection" and the term "parenteral" to mean "subcutaneously." D.I. 154 at 35. Because the Court concludes that neither term is limited to only subcutaneous injection, the Court need not address this argument.

The dictionary definitions uniformly support Novo's definition of "parenteral" as "taken into the body or administered in a manner other than through the digestive tract (*e.g.*, not by mouth or through the alimentary canal)." n49 Also, the dictionary definitions of "administer" support Novo's [*64] definition of "administer" as "to apply as a remedy." n50 Finally, the dictionary definitions of "patient" support the definition of "patient" as "an animal, including a human being, awaiting or under medical treatment." n51

n49 *See* Oxford Dictionary of Biochemistry and Molecular Biology 484 (1997) ("any route other than via the gastrointestinal tract, especially by injection"); Dictionary of Biochemistry and Molecular Biology 347 (2d ed. 1989) ("referring to the introduction of a substance into an animal organism by ways other than that of the digestive tract"); Merriam-Webster's New Collegiate Dictionary 844 (1981) ("introduced other than by way of the intestines"); Grant & Hackl's Chem. Dictionary 423 (1987) ("describing a route of administration of drugs or food, other than by mouth or into the intestine"); Webster's Third New Int'l Dictionary 1641 (1981) ("1: not intestinal: situated or occurring outside the intestine...2: injected or for injection subcutaneously, intramuscularly, or intravenously").

n50 *See* Merriam-Webster's Collegiate Dictionary 57 (10th ed. 1998) ("to give as a remedy"); Webster's Third New Int'l Dictionary 27 (1981) ("to give remedially (as medicine)"). There is no limitation in these dictionary definitions that administer be limited to only subcutaneous injection.

[*65]

n51 *See* Merriam-Webster's Collegiate Dictionary 863, 825 (10th ed. 1998) ("patient" means

"an individual awaiting or under medical care or treatment" and "individual" means "a particular being. . . as distinguished from a class"); Merriam-Webster's New Collegiate Dictionary 833 (1981) ("patient" means "an individual awaiting or under medical care or treatment"); Webster's Third New Int'l Dictionary 1152, 1655 (1981) ("patient" means "a sick individual" or "a client for medical services" and "individual" means "a particular being or thing as distinguished from a class"). These definitions are in no way limited to only human, and not animal, patients.

Other extrinsic evidence further supports the Court's definitions of these three terms. Regarding "parenteral" and "administer," both parties agree that, at the time of the invention, it was known in the art to administer insulin to diabetics intravenously. *See* Tr. at 422:5-424:22. In addition, Lilly's expert, Dr. Michael Weiss, testified that scientists have researched nasal and pulmonary administration of insulin to diabetics. *See id.* [*66] at 105:4-11. At the time the patent claims were written, one of ordinary skill in the art would have anticipated the use of the formulation by routes other than subcutaneous injection. It follows the terms "parenteral" and "administer" are not limited to subcutaneous injection.

Regarding the term "patient," extrinsic evidence supplied by both parties supports the Court's definition by showing that animals suffer from diabetes mellitus and are treated with injections of insulin. *See* Tr. at 65:17-66:11 98:21-101:7 (testimony of Lilly expert Dr. Weiss); 219:3-15 (testimony of Novo expert Dr. Dunn). Therefore, at the time of the invention, one of ordinary skill in the art could have anticipated that an insulin analog formulation would be administered to animals, as well as human patients.

As to all three terms, Lilly urges that the disclosure of preferred embodiments in the specification limits the definition of the terms. First, Lilly takes the position that "parenteral" is limited to subcutaneous injections because the specification only discloses formulations that have rapid action when injected subcutaneously. n52 Second, Lilly argues that the specification infers "administer" [*67] is limited to subcutaneous injections because the specification only discloses formulations that have rapid action when injected subcutaneously. n53 Finally, Lilly insists that "patient" is limited to humans because the specification only discloses using rapid acting human insulin analogs for human patients. n54

n52 *See* D.I. 173 at 26 (citing '978 patent at 1:15-18; 1:28-31; 1:34-38). At the *Markman* hearing, Lilly further argued that "parenteral" must mean "subcutaneous" because the rapid action of the patented invention is only needed for subcutaneous injection of the insulin analog. *See* Tr. at 420:5-20.

n53 *See* D.I. 173 at 26 (citing '978 patent at 1:15-18; 1:28-31; 1:34-38).

n54 *See* D.I. 173 at 25 (citing '978 Patent at 5:21; 1:23-25).

However, [HN18] the claims of the patent cannot be limited by disclosure of a preferred embodiment in the specification. *See Rhine v. Casio, Inc.*, 183 F.3d 1342, 1346 (Fed. Cir. 1999). The subcutaneous method of using the insulin analog [*68] formulations and the use on humans are only preferred embodiments disclosed in the specification. As to "parenteral" and "administer," if Lilly had desired to limit the claims to only "subcutaneous" injection, it could have done so by defining these terms to mean "subcutaneous injection" or by using the term "subcutaneous" in the claims. Likewise, if Lilly had desired to limit the claims to "human patients," it could have used that language instead of "patient." Since Lilly chose to use the broader terms "parenteral," "administer," and "patient," the scope of the claims should reflect its choice of words.

The Court holds "parenteral," "administer," and "patient" have the definitions discussed above.

V. Conclusion

In summary, the Court construes the disputed claim language as follows:

1. "human insulin analog complex" or "complex" (claims 1, 12) means an individual molecular structure, defined as "a chemical association state of two or more molecules held together by non-covalent bonds."

2. In claims 1 and 12, "hexamer" refers to the Zn-hIA structure, i.e., "a type of complex where six molecules of humin insulin analog are held together in a single structure." In claim 13, [*69] "LysPro-human insulin is a hexamer" is shorthand meaning "in the equilibrium, most of the LysPro-human insulin molecules are in Zn-hIA structures."

3. "formulation" (claims 2-11, 13) means "an equilibrium containing molecules and molecular structures."

4. "pharmaceutical" (claims 2-11, 13) means "containing a medicinal drug" where "medicinal drug" means "a substance or preparation used in treating disease."

5. "comprises" and "two zinc ions" (claim 1) means that the claimed human insulin analog complex can have other components in the complex, in addition to the

named components, but the named components, including the two zinc ions, must be in the specified amounts.

6. "consisting of" and "two zinc ions" (claim 12) indicates closed claim language and closes the claim to the inclusion of unrecited elements, except for impurities ordinarily associated therewith.

7. "wherein the human insulin analog is human insulin wherein Pro at position B28 is substituted with Asp, Lys, Leu, Val, or Ala, and Lys at position B29 is Lys or Pro; des(B28-B30)-human insulin; or des (B27)-human insulin" does not include a T[6] limitation;

8. "hexamer" (claims 1, 12, 13) does not include the R[6] [*70] limitation;

9. "parenteral" (claims 2-11, 13) means "taken or administered into the body by a means other than through the digestive tract."

10. "administering" (claim 10) means "to apply as a remedy."

11. "patient" (claim 10) means "an animal, including a human being, awaiting or under medical treatment."

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Rod segment, interstage quadrupole, with pin (2 each) 70111-20640
Lead, outer quadrupole 70111-20643
Lead, inner quadrupole 70111-20644
Rod, segment, interstage quadrupole (2 each) 70111-20645

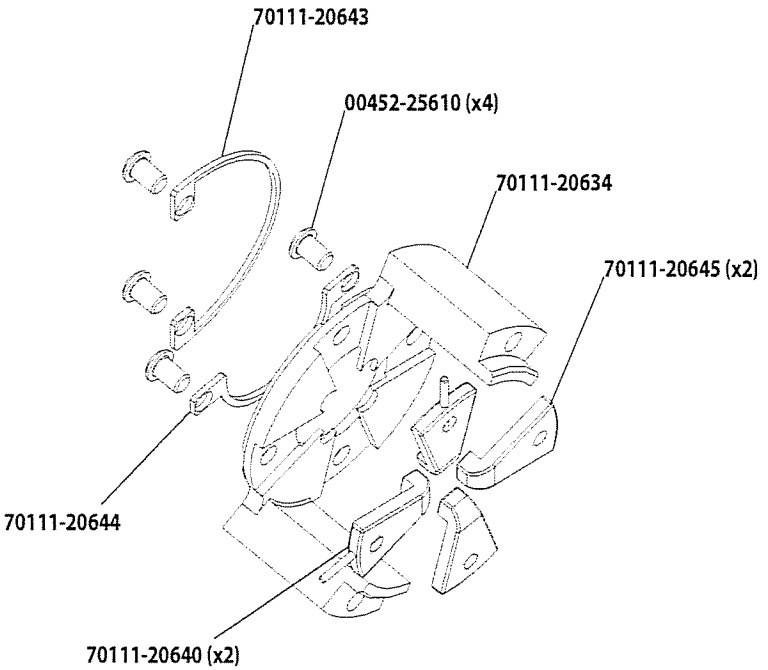

Figure 8-6. Q00 stack assembly part numbers

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QUADRUPOLE MASS SPECTROMETRY AND ITS APPLICATIONS

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CHAPTER V

FRINGING FIELDS AND OTHER IMPERFECTIONS

P.H. Dawson

In Chapter II, the principles of operation were described for quadrupole mass spectrometers with perfect fields; that is, with perfect geometry, perfectly sinusoidal applied voltages and without fringing fields. Imperfections in the quadrupole fields fall into three categories. The most important are imperfections caused by the presence of fringing fields at the ion entrance and ion exit. For the ion trap, ions are formed directly within the field and it is exempt from this problem. However, in the mass filter and monopole, fringing fields are always present to some extent. Fringing fields at the exit have not been examined in much detail, although special efforts are generally made to ensure collection of all exiting ions even if they are highly defocussed (see p. 34). The exact influence of fringing fields at the ion entrance is the subject of some debate. Some experimental evidence exists but more detailed measurements are needed. The fringing fields certainly become detrimental when the ions take more than three or four cycles to pass through. This is most likely to occur for low-energy and/or high-mass ions when one is attempting to obtain high performance. Various modifications to the ion entrance conditions have been proposed to avoid the problems (see Appendix F), a notable example being the "delayed d.c. ramp" of Brubaker [1] which is described below. Most calculations of fringing fields have been made by the computation of ion trajectories in the xz or yz planes in monotonically increasing fields. Such calculations have proved very useful although they involve some significant approximations. The results suggest that short fringing fields play an important role in the functioning of the monopole and a sometimes beneficial role in normal mass filter operation. The limited experimental evidence supports the general conclusions of the calculations. Recently, fringing fields have been incorporated in a phase-space dynamics approach, which should permit much better ion source evaluation and design.

The second type of imperfection results from systematic field faults which can be represented by modifications to eqn. (2.6) for the potential. These may be geometric faults caused by slight misalignment of the electrodes, by mis-shaping of the electrodes, or by modification of the field due to the electrode housing or to nearby insulators. Systematic faults may also result from harmonics mixed in with the fundamental frequency of the applied rf. Most

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of the systematic faults become more important as a higher performance is demanded. They take an added significance the longer the time the ions spend within the field and the closer one operates to the limits of the stability diagram. The influence of such field faults has been extensively studied, both by analysis of the equations of motion and by the examination of ion trajectories. The experimental evidence supporting the calculations is quite strong.

The third type of imperfection is a local imperfection of the field, due, for example, to local contamination of an electrode surface or to exposure of some insulator surface. Such surfaces build up charges which perturb the nearby field. Evidently, these localized problems cannot be dealt with in a general way. They should, however, be less important than systematic faults which perturb the ion trajectory throughout its length.

A. FRINGING FIELDS

For the mass filter and the monopole, as for many other types of mass spectrometer, the inevitable presence of fringing fields poses some difficult problems, but also presents opportunities for improving instrument performance. Brubaker was the first to consider fringing fields in detail. Examining the angular acceptance of a mass filter intended for space applications, he found it was particularly poor in the yz plane [2]. While approaching the mass filter entrance, ions are subjected to weaker fields represented, for example, by (a, q) values distributed along the operating line from the origin to the stability tip (see Fig. 2.10). These lower (a, q) values represent regions of incipient instability for trajectories in the yz plane (but not for the xz plane). If the ions spend a large number of rf cycles passing through the fringing fields, the y displacements become very great by the time the ions enter the full field of the mass filter. To avoid the ions passing through the region of instability, Brubaker [1, 3] has developed various modifications of mass filter entrance conditions. They are generally referred to as the "delayed d.c. ramp". The delayed d.c. ramp has been used successfully by Brubaker but has not found general application (see Chapter VI, p. 144).

There are some other more subtle effects of fringing fields. Even very short fringing fields drastically modify the relationship of maximum ion displacement to initial phase (see Chapter II, p. 24), and also change the acceptance ellipses of the mass filter (p. 26). It is this modification that can be beneficial in the case of the mass filter and may be of vital importance in the monopole. The potential advantages of short fringing fields were evident in trajectory calculations by Brukaker [1] and have been further examined by Dawson [4–7]. The phase-space approach [8] is more useful in predicting the mass filter acceptance in the presence of various fringing fields and in evaluating ion source designs for compatibility.

The weaknesses of the calculations lie in the assumptions that in the

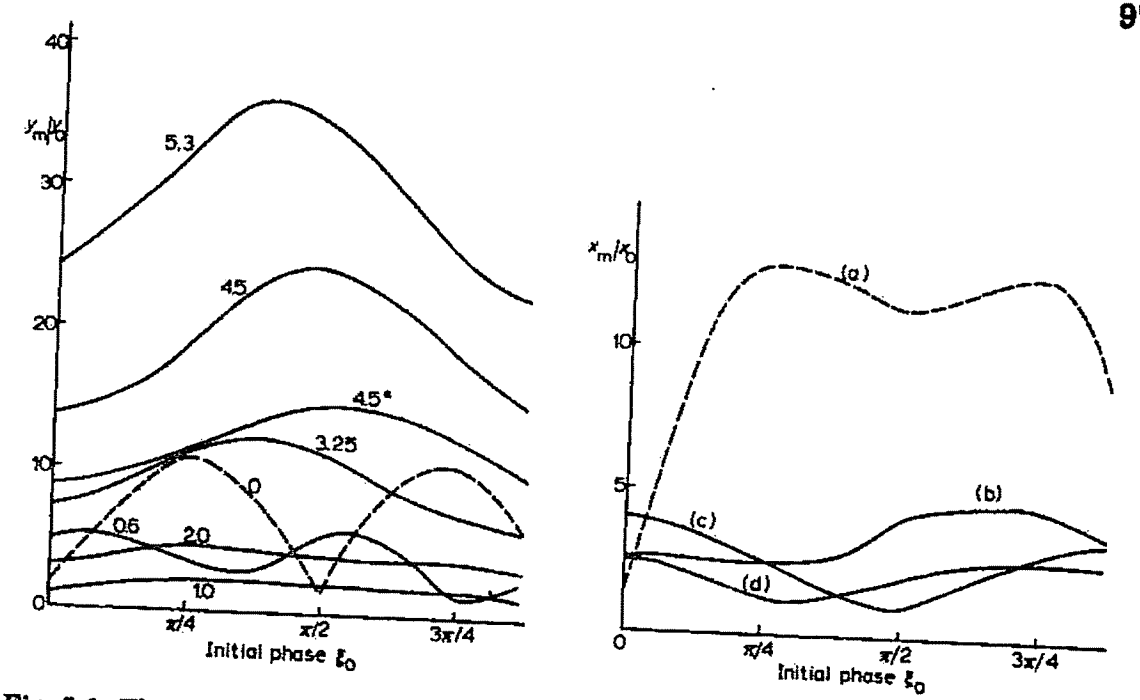

Fig. 5.1. The maximum y displacement in the mass filter as a function of the initial phase for the point $a = 0.228$ $q = 0.7$. The length of the assumed linear fringing field is given on each curve. The curve marked 4.5* was for a quadratically increasing field. The initial ion direction was assumed parallel to the instrument axis.

Fig. 5.2. The maximum x displacement as a function of the initial phase for the point $a = 0.228$ $q = 0.7$ assuming no initial x direction velocity. (a) Zero fringing field; (b) 2 cycle coincident rf and d.c. linear fringing fields; (c) 4.5 cycle coincident rf and d.c. linear fringing fields; (d) 4.5 cycle rf and d.c. fringing fields, the d.c. being delayed by 1.6 cycles.

fringing field region, the motion in the x and y directions remains independent, that the field in the z direction is zero, and that the x and y fields increase in some mathematically convenient way (linearly or quadratically) as one approaches the mass filter entrance. There is, however, a particular form of fringing field which is amenable to the calculation of the coupled trajectories in three dimensions and this has recently been used to establish limits for the validity of the two-dimensional linear approximations [8].

(1) *The mass filter*

The ion trajectories for the yz plane that are illustrated later (Fig. 5.14) for different initial phases of the rf field demonstrate the modification caused by a short fringing field [6] (compare with illustrations in Chapter II). The gradual entry into the field seems to produce a near equivalence for all initial phases. Figure 5.1 shows the effect on the maximum y displacement as a function of initial phase for various linearly increasing entrance "ramps" [6] calculated for an ion beam approaching the mass filter parallel to its axis. The number on each curve indicates the length in rf cycles of the fringing field. Fringing fields as short as 0.6 rf cycles have a profound influence and fields up to about

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